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616 61Y 635 636 637 63Y 640 64Y 650 654
65Y 660 664 66Y 670 674 67Y 77Y

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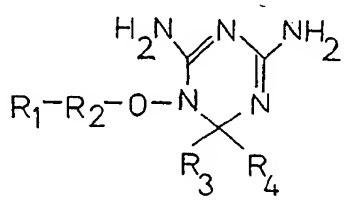
(54) DI-HYDRO TRIAZINE DERIVATIVES AND PROCESSES FOR THEIR MANUFACTURE

(71) We, BEECHAM GROUP LIMITED, a British Company, of Beecham House, Great West Road, Brentford, Middlesex, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

This invention relates to N-substituted symmetrical di-hydrotriazine derivatives and to processes for making them. Compounds within the scope of the present invention have anti-microbial activity of various kinds, including anti-malarial activity.

Accordingly the present invention provides novel N-substituted symmetrical di-hydrotriazine derivatives



I

where R_1 is an aromatic ring system, a heterocyclic group or a non aryl carbocyclic ring system of 3—8 carbon atoms, all of which rings may be substituted or unsubstituted;

R_2 is a substituted or unsubstituted divalent aliphatic group of 2—16 carbon atoms;

R_3 is hydrogen or lower alkyl of 1—4 carbons, and R_4 is lower alkyl of 1—4 carbon atoms, where R_3 and R_4 may be the same or different and may be linked to form a spirocycloalkane or loweralkylspirocycloalkane group including the 2-carbon of the triazine ring

and salts and acyl derivatives thereof, except that R_1 is not an unsubstituted phenyl group when R_2 is unsubstituted and that R_1 is not 1 - methyl - 2 - naphthyl when R_2 is ethylene.

Within the definition of R_1 we wish to include: aryl, including partially hydrogenated aryl and polycyclic aryl, cycloaliphatic, including saturated and unsaturated cycloaliphatic and heterocyclic groups.

R_1 may for example be phenyl, naphthyl, phenanthryl, pyrenyl, anthryl, tetrahydronaphthyl and tetrahydrophenyl; cycloalkyl, including cyclopentyl, cyclohexyl, cycloheptyl and methylcyclohexyl; cycloalkenyl, including

cyclohexenyl, heterocyclic, including pyridyl, pyrrolidinyl, piperazinyl, imidazoyl, benzimidazoyl, phthalimido, quinolyl, furyl and thienyl.

The group R_1 may have a wide range of substituents: it may for example, where the nature of R_1 itself is appropriate be mono- or poly-substituted by hydrocarbon groups e.g. aryl; alkyl, including methyl and ethyl; cycloalkyl of 3—8 carbon atoms including cyclohexyl, cyclopentyl and cycloheptyl; halogen, including chlorine and bromine; nitro; halogeno-lower alkyl, including mono-, di- and tri-chloro-, fluoro- or bromo- lower alkyl; lower alkoxy including methoxy, ethoxy and propyloxy; lower alkoxy carbonyl, including methoxycarbonyl, ethoxycarbonyl and propyloxycarbonyl; aryllowеralkyl, including benzyl and phenylethyl; carboxy; hydroxyl; mercapto; cyano; loweralkylthio, including methylthio and ethylthio; loweralkyl sulphonyl; alkoxysulphonylalkyl; hydroxy-loweralkyl, including 2-hydroxyethyl; loweralkoxy alkyl; cyano-loweralkyl; sulphonamido; amino and mono- and di-loweralkylamino, including methyl- and ethyl- amino. When R_1 has more than one substituent these may be the same or different. In general unless otherwise specified these groups may have 1—24 carbon atoms if the prefix "lower" is not used and 1—6 carbon atoms if the prefix "lower" is used.

Within the definition of R_2 we wish to include straight chain or branched divalent aliphatic groups both saturated and unsaturated. R_2 may for example be propylene, vinylene, 3-methylpropylene, $-(CH_2)_n-$ where n is 1—16, but is preferably a straight chain alkylene of 2—8 carbon atoms, e.g. tetramethylene.

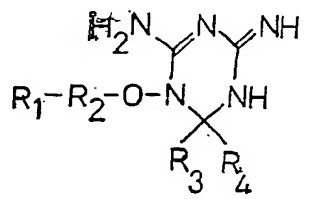
R_2 may be mono- or poly- substituted for example with hydroxy, lower alkoxy of 1—6 carbon atoms or halogen.

One preferred group of compounds are those of the general formula I wherein R_1 is a substituted aryl ring system (except when R_2 is substituted or unsubstituted) or a substituted or unsubstituted heterocyclic group or a substituted or unsubstituted cycloalkyl group of 3 to 8 carbon atoms and R_2 is a divalent aliphatic hydrocarbon radical containing 2 to 16 carbon atoms which may be straight chain or branched and mono or poly substituted by hydroxyl, methoxy, or halogen which may be the same or different.

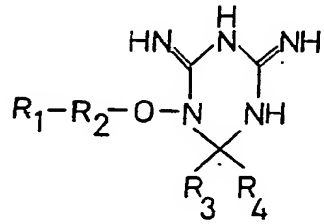
R_3 and R_4 may for example be methyl, hydrogen and ethyl or may be linked to form a spirocycloalkane group including the 2-carbon atom of the triazine ring for example spirocyclohexane or 4-methylspirocyclohexane.

Although formulae have been used herein in order to represent the compounds of the present invention, the value of the present invention does not depend upon the precise theoretical correctness of these formulae. The names and formulae used herein are not intended to limit the invention to any specific tautomeric form or to any specific optical or geometric isomer.

Structures of the following form may for example contribute towards formula I.



Ia



Ib

The compounds of the present invention are conveniently prepared in the form of acid addition salts, since the free base tends to be somewhat unstable, and a wide range of acids may be used. If the compounds are to be applied pharmaceutically, then the acid should of course have acceptable pharmaceutical properties such as low toxicity.

Thus the compounds of the present invention may be made in the form of the monohydrohalic acid addition salts for example the hydrobromide or the hydrochloride. Other salts may be made however by simple reaction of base with acid and may be desirable in order to modify the properties of the product such as its toxicity, taste, physical form or rate of release into the body. For example the compounds may be made in the form of the picrate, saccharinate, acetate, acid maleate, acid phthalate, succinate, phosphate, *p*-nitrobenzoate, stearate, mandelate, N-acetyl-glycine, pamoate, cyclohexyl sulphamate, citrate, tartrate, or gluconate.

Stable salts are normally formed with a ratio one molecule of triazine to one molecule of monobasic acid (or more than one molecule of triazine in the case of polybasic acids) but the possibility of having basic groups as substituents in R_1 for example means that further quantities of acid may be combined with the triazine in some cases.

The presence of the amino groups on the triazine ring of formula I creates the possibility of forming acyl derivatives by reaction with acylating agents such as acyl halides, anhydrides and acyl azides. One to four acetyl groups for example may be associated with the compound of formula I although in some cases it may be more difficult to make derivatives having higher numbers of acetyl groups.

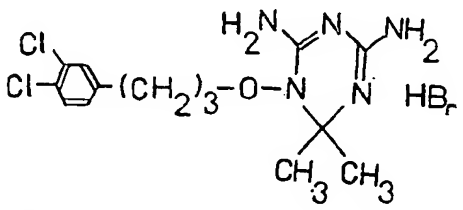
The present invention therefore includes compounds of formula I in the form of acyl derivatives (for example loweraliphatic acyl, such as acetyl derivatives or benzoyl).

In certain preferred compounds of the present invention R_1 is phenyl or naphthyl substituted by one or more halogen atoms, especially chlorine. Preferably also R_2 is a saturated aliphatic group containing 2—8 carbon atoms and R_3 and R_4 are both methyl.

Compounds within the scope of the present invention have activity against bacteria, protaozoa, parasites, including the Plasmodia of malaria, fungi including dermatophytes and *Candida*, and also display coccidiostatic properties in certain cases.

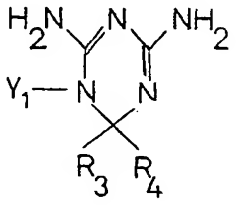
Thus activity has been observed against *Staph. aureus, Escherichia coli, Candida albicans, Proteus mirabilis, Pseudomonas pyocyanea and Streptococcus haemolyticus*.

For example 4,6 - diamino - 1,2 - dihydro-2,2 - dimethyl - 1 - [3 - (3,4 - dichlorophenyl)propyloxy] - 1,3,5 - triazine hydrobromide of formula



displays activity against cycloguanil-sensitive and cycloguanil-resistant strains of *Plasmodium berghei* in the mouse.

The present invention also provides a process for the preparation of the compounds of the present invention which comprises reacting a triazine



III

where Y_1 is a reactive group with a compound R_3Y_2 which is capable of reacting with Y_1 so as to form the group R_1R_2O— or an intermediate group capable of conversion thereto and where necessary converting the intermediate group to R_1R_2O— and optionally where necessary forming a salt.

Preferably Y_1 and Y_2 are OH or derivatives of OH capable of reacting with each other to form an oxygen linkage. Thus at least one of Y_1 and Y_2 should contain an oxygen atom. Conveniently Y_1 is OH (see formula VI) or OM where M is a metal for example sodium, potassium or lithium and Y_2 is chlorine, bromine or iodine. Other reactive derivatives of the OH group include sulphonic acid derivatives.

In a preferred process a compound R_1R_2Z where Z is chlorine or bromine is reacted with the hydroxy triazine VI in an inert solvent or diluent. Examples of suitable solvents include dimethyl sulphoxide, dimethylformamide or ethanol.

The hydroxy triazine derivative VI is usually obtained in the form of an acid addition salt (e.g. the hydrochloride) from which the free base may be liberated by one equivalent of base such as an alkali metal hydroxide (e.g. potassium hydroxide) or sodium in ethanol or methanol. The mixture may then be evaporated and reacted in a suitable solvent (e.g. dimethylformamide or dimethylsulphoxide). Preferably extra base is not added, since with two equivalents of sodium in alcohol for example a less pure product is obtained.

In a modified procedure, usually giving poorer yields, the hydrochloride of compound VI in dimethylformamide or dimethylsulphoxide is reacted with one equivalent of aqueous potassium hydroxide (using as little water as possible) and the resulting mixture reacted to give a triazine hydrohalide.

The Y_1 N-substituted triazine III may be made from an appropriately substituted diguanide as outlined hereinafter or by any other convenient method.

The side-chain R_1R_2—O may be attached in a variety of ways and may be attached in one reaction or in a multi stage process. Normally the minimum number of stages is employed to achieve optimum yields, for convenience and other factors.

Thus well-known ether-forming synthetic methods may be used to link the side-chain to the triazine with the O atom previously in place on either the side-chain or the triazine. Typical examples are

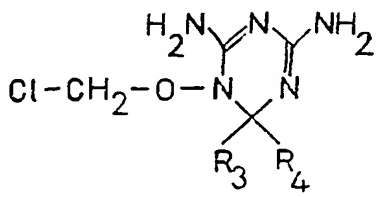
1. the reaction of a halide with a hydroxyl compound with or without added base as previously described.

2. the reaction of a reactive ester such as a sulphonate with a hydroxyl compound.

In another process a compound of general formula

$$R_1—R_2'—CH=CH_2$$

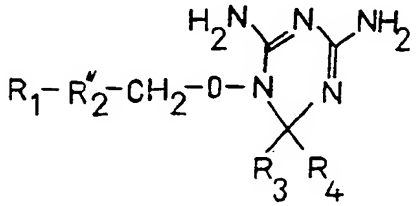
may be reacted with the hydroxy triazine VI where R_2' is R_2 in formula I minus two carbon atoms. Alternatively compounds within the scope of the present invention may be made by reacting the hydroxytriazine VI with formaldehyde in the presence of hydrochloric acid to form a compound of formula



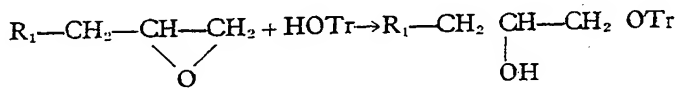
and reacting this with a compound of formula

$$R_1—R_2'' \text{ Mg halogen}$$

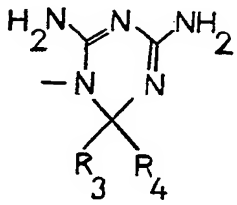
where R_2'' is R_2 in formula I minus one carbon atom, to form compounds of general formula



Alternatively certain hydroxy substituted compounds within the scope of the present invention may be made by reacting an appropriately substituted ethylene oxide with the hydroxy triazine VI as illustrated by the reaction scheme

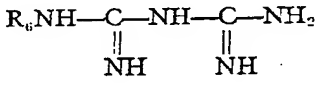


where Tr is used to represent



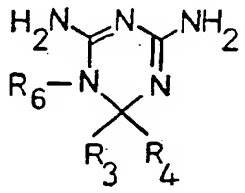
Reactions of the types illustrated above may clearly be performed using either the hydroxy-triazine VI as a starting material or a triazine with a partial side-chain already in place although in many cases such a partial side-chain triazine may be made from the hydroxy-triazine originally.

A further aspect of the present invention provides a process for the preparation of the compounds of the present invention which comprises reacting a substituted diguanide of formula



IV

where R_6 is $R_1—R_2—O—$ or a group capable of conversion thereto with a carbonyl compound $R_3 . CO . R_4$ in the presence of an acid catalyst to form a substituted triazine of formula V



V

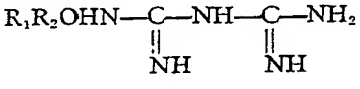
and converting R_6 where necessary into

$$R_1—R_2—O—$$

and optionally where necessary forming a salt.

Preferably the acid is a strong acid such such as hydrochloric or formic acid and at least one molecular equivalent is used. The reaction may in some cases be carried out without any further solvents or diluents but usually an inert solvent such as a lower aliphatic alcohol (e.g. methanol) is preferred.

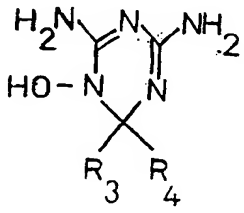
When R_6 is $R_1—R_2—O—$ the substituted diguanide II becomes



IVa

and accordingly the present invention also provides compounds of this kind for use as intermediates in the process of the present invention. Compound IVa may be made for example by reacting a bromide of general formula R_1R_2Br with benzohydroxamic acid and treating this with acid to form an oxy-amine of formula $R_1R_2ONH_2$ which is subsequently reacted with dicyandiamide.

Alternatively the group R_6 may be chosen so as to be convertible into the group R_1R_2O. For example R_6 may be a group which is capable of undergoing catalytic hydrogenolysis. Thus R_6N-substituted triazine may be formed from an appropriately substituted diguanide and then hydrogenolysed to produce the hydroxy triazine VI



VI

R_6 may for example be substituted or unsubstituted benzyloxy or substituted or unsubstituted naphthylmethyloxy and the hydrogenolysis may be carried out with hydrogen in the presence of a palladium catalyst.

The hydroxytriazine VI may then be reacted in a variety of ways well understood by those skilled in the art and as indicated previously to produce the desired substituted triazine of formula I. A preferred method is to react VI with a compound $R_1R_2Y_3$ where Y_3 s a reactive group displacable by a nucleophilic group.

It will be further understood by those skilled in the art that the side-chain R_2—R_2—O may be built up or attached in stages either before or after the substituted diguanide IV is converted to the substituted triazine V.

The final product may be obtained in the form of an acid addition salt as a consequence of the reaction without the necessity of a separate step of salt formation but if necessary the additional step of reacting the free base with an acid to form a salt may be performed. Salts can be converted back to the free base by treatment with alkali (e.g. KOH) and then converted to other salts as required by conventional means.

Acyl derivatives may also be made by reacting the base with acyl derivatives as previously described.

The present invention also provides pharmaceutical compositions for use against malaria comprising as active ingredient a compound according to the present invention together with a pharmaceutically acceptable carrier.

Thus the active compounds of this invention may be employed for the treatment and prevention of malaria in man. Therefore, one aspect of the present invention is a method of treatment or prevention of malaria in man which comprises administering one of the active compounds to the person infected or at risk. The compound may be administered orally, parenterally, or by suppository, though the oral route is preferred.

As stated above the compound of this invention may be administered orally, parenterally or by suppository. The water solubility of the hydrochloride of the compound and most other salts is low and the hydrochloride is non-hygroscopic. If solutions are required it will be necessary to add solubilising agents to the water, choose non-aqueous solvents, find a more soluble salt or prepare very dilute solutions.

Oral formulations are preferred and with the above proviso in connection with solutions, typical oral formulations will include tablets, pills, capsules, sachets, granules, powders, chewing gum, suspensions, emulsions and solutions: particularly preferred oral formulations are tablets and capsules. Where appropriate and where necessary the formulations may include diluents, binding agents, dispersing agents, surface-active agents, lubricating agents, coating materials, flavouring agents, colouring agents, solvents, thickening agents, suspending agents, sweeteners or any other pharmaceutically acceptable additives, for example gelatin, lactose, starch, talc, magnesium stearate, hydrogenated oils, polyglycols and syrups. Where the formulations are tablets or capsules and the like they will represent pre-measured unit doses but in the case of granules, powders, suspensions and the like the formulations may be presented as pre-measured unit doses or in multi-dose containers from which the appropriate unit dose may be withdrawn.

The injectable form may be an aqueous or non-aqueous solution, suspension, or emulsion in a pharmaceutically acceptable liquid (e.g. sterile pyrogen-free water or parenterally acceptable oils) or mixture of liquids which may contain bacteriostatic agents, antioxidants or other preservatives, buffers, (preferably in the physiological pH range of 6.5—7.0), solutes to render the solution isotonic with the blood, thickening agents, suspending agents or other pharmaceutically acceptable additives. Such forms will be presented in unit dose form such as ampoules or disposable injection devices or in multi-dose forms such as a bottle from which the appropriate dose may be withdrawn, or as a solid form or concentrate which can be used to quickly prepare an injectable formulation. All formulations for injection are preferably rendered sterile. Suppositories containing the compound will also contain suitable carriers (e.g. cocoa butter or polyglycols).

In addition to standard pharmaceutical additives there may be included within formulations of the compound other therapeutic agents, particularly including other antimalarials (e.g. sulphonamides).

Examples of the invention will now be described:

EXAMPLE 1

4,6 - diamino - 1,2 - dihydro - 2,2 - dimethyl-1 - [3 - (3,4 - dichlorophenyl)propyloxy]-1,3,5 - triazine hydrobromide

Benzhydroxamic acid (137 g. 1.0 mol.) and I.M.S. (a mixture of ethanol with a few % methanol) (1.5 litres) are placed in a flask equipped with a stirrer, dropping funnel and condenser, and stirred until solution is complete. A solution of NaOH (40 g., 1.0 mol.) in water (100 ml.) is added with vigorous stirring. The sodium salt of benzhydroxamic acid may precipitate at this stage.

Benzyl bromide (170 g., 120 ml.) is added dropwise over 45 minutes, the mixture gradually becomes clear, leaving only a small amount of inorganic material undissolved. The reaction is preferably left at room temperature for 3 days, refluxing for 1—2 hours will give slightly lower yields.

The solvent is removed under reduced pressure and the oily residue is dissolved in ethyl acetate and washed several times with water. The solvent extract is dried with magnesium sulphate, filtered and evaporated to dryness under vacuum.

The solid residue is triturated with ether and collected to give the required benzyl benzhydroxamate ($C_6H_5CONHOCH_2C_6H_5$) m.p. 100—102°C.

The benzyl benzhydroxamate (170 g.) is dissolved in methanol (500 ml.) and concentrated hydrochloric acid (165 ml.) is added. The mixture is refluxed for 3 hours, filtered hot, and allowed to crystallise. The solid collected by filtration is washed well with ether, until no smell of methyl benzoate remains. Yield of amino-oxymethylbenzene hydrochloride:

First crop 120 g. m.p. 227—230° (sealed tube). Concentration of the mother liquors and treatment with ether gives a further crop, 20 g. m.p. 220—225° (sealed tube).

Total yield=140 g. (ca. 90%).

Amino oxymethyl benzene hydrochloride (97.5 g.) and dicyandiamide (51.4 g.) are dissolved in I.M.S. (300 ml.) with stirring and warming. The mixture is then refluxed for 3 hours, filtered if necessary, and evaporated under reduced pressure. The oily residue is dissolved in water and treated with strong aqueous NaOH (ca. 6N) with stirring. The diguanide base which separates, solidifies on cooling and is collected, washed with water and dried.

The yield of benzyloxy diguanide base is 95—100 g. m.p. 98—100° (80%).

Benzyloxydiguanide base (52 g.) is dissolved in I.M.S. (200 ml.) and concentrated hydrochloric acid (43 ml.) is added, followed by acetone (200 ml.). Preferably, the reaction is left at room temperature for 3 days but a 2—3 hour reflux period will give slightly lower yields. Some triazine usually separates, and may be collected by filtration, washed with water and dried.

The mother liquors are evaporated to dryness and the residue triturated with acetone, to give a white solid. The solid is collected washed with water and dried.

Total yield of 4,6 - diamino - 1,2 - dihydro-2,2 - dimethyl - 1 - benzloxy - 1,3,5 - triazine hydrochloride 61 g. m.p. 204—206° (80%).

41 parts of 4,6 - diamino - 1,2 - dihydro-2,2 - dimethyl - 1 - benzyloxy - 1,3,5 - triazine hydrochloride dissolved in 320 parts of ethanol and 220 parts of water was shaken with hydrogen and 0.25 to 1.0 parts of 10% palladised charcoal catalyst, that is a catalyst composed of acid washed active charcoal (90 parts) on which has been adsorbed ten parts by weight of metallic palladium in a finely divided form, at room temperature and atmospheric pressure until the uptake of hydrogen ceased. The catalyst was filtered off and the filtrate evaporated to dryness to give 4,6 - diamino - 1,2-dihydro - 2,2 - dimethyl - 1 - hydroxy - 1,3,5-triazine hydrochloride (24.5 parts), m.p. 234—235°C (decomp.).

Crystallisation from ethanol gave needles, m.p. 237°C (decomp.). The production described in this Example may be effected using a platinium catalyst as described below:

11 Parts of 4,6 - diamino - 1,2 - dihydro-2,2 - dimethyl - 1 - benzyloxy - 1,3,5 - triazine hydrochloride dissolved in 200 parts methanol and 100 parts water were shaken with hydrogen and platinic oxide at room temperature and atmospheric pressure until a 10% excess over the theoretically calculated hydrogen uptake was observed. Hydrogenation was stopped, the catalyst removed and the clear filtrate evaporated to dryness at reduced pressure. The solid residue was triturated with acetone and the 4,6 - diamino - 1,2 - dihydro-2,2 - dimethyl - 1 - hydroxy - 1,3,5 - triazine hydrochloride collected in theoretical yield, m.p. 234° (decomp.).

4,6 - Diamino - 1,2 - dihydro - 2,2 - dimethyl - 1 - hydroxy - 1,3,5 - triazine hydrochloride (1.93 g.) dissolved in methanol (25 ml.) was treated with a solution of KOH (0.7 g.) in methanol (15 ml.). The mixture was refluxed for 20 minutes and the solvent removed at reduced pressure. The residue was suspended in dimethylformamide, and treated with 3 - (3,4 - dichlorophenyl)propyl bromide (3.0 g.). The mixture was stirred at room temperature for one hour, and then gently warmed until a clear solution was obtained. The solution was filtered, and evaporated to dryness, the residue was triturated with acetone, and the white solid collected, (3.2 g.) m.p. 190—193. This material was washed with water and recrystallised from ethanol to give the pure triazine (1.7 g.) m.p. 203°C, 4,6 - diamino-1,2 - dihydro - 2,2 - dimethyl - 1 - [3 - (3,4-dichlorophenyl)propyloxy] - 1,3,5 - triazine hydrobromide.

EXAMPLE 2

4,6 - Diamino - 1,2 - dihydro - 2,2 - dimethyl-1 - (6 - (cyclohexyl)hexyloxy) - 1,3,5-triazine hydrobromide

6 - (Cyclohexyl) - hexyl bromide was prepared by the treatment of 6 - (cyclohexyl)-hexan - 1 - ol with a mixture of HBr (48%) and H_2SO_4 (28:3 parts by volume). The mixture was refluxed for 6 hours, diluted with water, and extracted with ether. The extract was washed with water, dilute $NaHCO_3$ solution and water, dried over $MgSO_4$. After filtration and removal of the solvent, the oily residue was distilled at 1 mm. pressure. The fraction boiling at 112—114°C was the required bromide n_D^{23} 1.4840.

The above bromide (7.5 g.) was reacted with the base derived from 4,6 - diamino - 1,2-dihydro - 2,2 - dimethyl - 1 - hydroxy - 1,3,5-triazine hydrochloride (5.8 g.) and KOH (2.1 g.) as described above. The reaction was heated with stirring at 90—100° for 6 hours. After working up in the previously described manner, the required triazine was obtained (5.0 g.) m.p. 203°C, 4,6 - diamino - 1,2 - dihydro - 2,2 - dimethyl - 1 - (6 - (cyclohexyl)-hexyloxy) - 1,3,5 - triazine hydrobromide.

EXAMPLES 3—41

The following compounds were made by a process closely similar to that described in Example 2. Symbols have the meanings ascribed to them in formula I.

Ex. No.	R_1	R_2	R_3	R_4	Salt	m.p. °C.
3	3,4—$Cl_2C_6H_3$	$(CH_2)_2$	CH_3	CH_3	HBr	216
4	3,4—$Cl_2C_6H_3$	$(CH_2)_3$	CH_3	CH_3	HBr	203
5	4—ClC_6H_4	$(CH_2)_2$	CH_3	CH_3	HBr	210
6	C_6H_5	$CHCl.CHCl.CH_2$	CH_3	CH_3	HBr	187
7	4—$NO_2C_6H_4$	$(CH_2)_3$	CH_3	CH_3	HCl	206
8	N-Pyrrolidyl	$CH(CH_3)CH_2$	CH_3	CH_3	HCl	183—185
9	N'-Methyl-N-piperazinyl	$CH(CH_3)CH_2$	CH_3	CH_3	HCl	153—155
10	4—Cl C_6H_4	$(CH_2)_3$	CH_3	CH_3	HBr	190—192
11	Cyclohexyl	$(CH_2)_6$	CH_3	CH_3	HBr	203
12	Cyclohexyl	$(CH_2)_6$	—$(CH_2)_5$—		HBr	225—226
13	3,4—$Cl_2C_6H_3$	$(CH_2)_4$	CH_3	CH_3	HBr	225
14	2—CH_3—5—NO_2—imidazolyl	$(CH_2)_2$	CH_3	CH_3	HCl	193
15	4-Pyridyl	$(CH_2)_3$	CH_3	CH_3	HBr	200
16	Cyclohexyl	$(CH_2)_3$	CH_3	CH_3	HBr	186
17	Cyclohexyl	$(CH_2)_3$	—$(CH_2)_5$—		HBr	242
18	2,6—$Cl_2C_6H_3$	$CH(CH_3)$	CH_3	CH_3	HBr	216
19	2,4—$Cl_2C_6H_3$	$CH(CH_3)$	CH_3	CH_3	HBr	201
20	3,4—$Cl_2C_6H_3$	$CH(CH_3)$	CH_3	CH_3	HBr	214—216
21	3,4—$Cl_2C_6H_3$	$CH(C_2H_5)$	CH_3	CH_3	HBr	209—210
22	2,4—$Cl_2C_6H_3$	$CH(C_2H_5)$	CH_3	CH_3	HBr	201—202
23	2,6—$Cl_2C_6H_3$	$CH(C_2H_5)$	CH_3	CH_3	HBr	185—187

Ex. No.	R_1	R_2	R_3	R_4	Salt	m.p. °C.
24	2,4—$Cl_2C_6H_3$	$CH(C_2H_5)$	H	C_2H_5	HBr	188—190
25	2,6—$Cl_2C_6H_3$	$CH(C_2H_5)$	H	C_2H_5	HBr	185—187
26	3,4—$Cl_2C_6H_3$	$CH(CH_3)$	H	C_2H_5	HBr	213—215
27	2,4—$Cl_2C_6H_3$	$CH(CH_3)$	H	CH_3	HBr	225—227
28	3,4—$Cl_2C_6H_3$	$CH(CH_3)$	H	CH_3	HBr	225—227
29	2,4—$Cl_2C_6H_3$	$CH(CH_3)$	H	C_2H_5	HBr	188—190
30	2,6—$Cl_2C_6H_3$	$CH(CH_3)$	H	C_2H_5	HBr	217—219
31	2-Benzimidazolyl	$(CH_2)_3$	CH_3	CH_3	2.HBr 1.H_2O	246—247
32	3,5—$(CH_3)_2$—Phenyl	$(CH_2)_3$	CH_3	CH_3	HBr	233—235
33	4—NH_2—Phenyl	$(CH_2)_2$	CH_3	CH_3	HBr	215
34	N-Phthalimido	$(CH_2)_2$	CH_3	CH_3	HBr	201—203
35	N-1,2,3,4-Tetrahydro-*iso* quinoline	$(CH_2)_2$	CH_3	CH_3	2.HBr	ca 100
36	*cyclo*Hexyl	$(CH_2)_4$	CH_3	CH_3	HBr	196—198
37	3—CF_3Phenyl	$(CH_2)_3$	CH_3	CH_3	HBr	185
38	1-Naphthyl	$(CH_2)_2$	CH_3	CH_3	HBr	220—222
39	3,4—Cl_2Phenyl	CH=CH—CH_2	CH_3	CH_3	HBr	209
40	1—Cl—2-naphthyl	$(CH_2)_3$	CH_3	CH_3	HBr	194—196
41	2,4—Cl_2—phenyl	CH=CH—CH_2	CH_3	CH_3	HBr	190—191

EXAMPLE 42

4,6 - Diamino - 1,2 - dihydro - 2,2 - dimethyl-1 - [3 - (3,4 - dichlorophenylpropyloxy)]-1,3,5 - triazine hydrochloride

Benzhydroxamic acid (13.7 g.) was dissolved in methanol (100 ml.) and a solution of NaOH (4.0 g.) in 10 ml. of water was added. 3 - (3,4-dichlorophenyl)propyloxy bromide (26.8 g.) was added dropwise with stirring. When the addition was complete the mixture was refluxed for 3 hours, the solvent evaporated and the residue dissolved in water and extracted with ethyl acetate. The solvent extract was washed with water, dried and evaporated to yield a pale yellow viscous oil which slowly crystallised. The required benzhydroxamate was obtained by trituration with ether and filtration to give a white solid which could be crystallised from ethanol to yield the pure compound.

3 - (3,4 - dichlorophenyl)propyl benzhydroxamate (16.2 g.) was refluxed with a mixture of methanol (120 ml.) and concentrated hydrochloric acid (40 ml.) for 2 hours. The reaction mixture was filtered and evaporated under reduced pressure and the residue was triturated with ether, filtered and washed well with ether to yield 3- (3,4 - dichlorophenyl)propyloxyamine hydrochloride. This compound (12.8 g.) and dicyandiamide (6.3 g.) were dissolved in ethanol (100 ml.) and refluxed for 3 hours. The reaction mixture was evaporated to dryness under reduced pressure and the residual gum was dissolved in water and basified with 4N NaOH solution: an oil separated which slowly solidified. The solid was collected by filtration, washed well with water and dried in a vacuum desiccator. The 3 - (3,4 - dichlorophenyl)propyloxy diguanide thus obtained was a cream coloured solid

which darkened on prolonged exposure to light. The crude material could be recrystallised from ethyl acetate/petrol to yield the pure compound.

15.2 g. of the pure compound was dissolved in methanol (50 ml.) and 8.6 ml. of concentrated hydrochloric acid was added followed by 50 ml. of acetone and the mixture refluxed for 3 hours. The reaction mixture was filtered and evaporated to dryness under reduced pressure, the residue was titurated with acetone and filtered. The white solid obtained was washed well with water, dried and recrystallised from ethanol to yield 4,6 - diamino - 1,2-dihydro - 2,2 - dimethyl - 1 - [3 - (3,4 - dichlorophenyl)propyloxy] - 1,3,5 - triazine hydrochloride, m.p. 235—237°C (decomp.).

EXAMPLE 43

Acyl derivatives of 4,6 - diamino - 1,2-dihydro - 2,2 - dimethyl - 1 - [3 - (3,4-dichlorophenyl)propyloxy]-1,3,5-triazine

a) *Diacetyl derivative*

The triazine of the title (1.0 g.) and redistilled acetic anhydride (10 ml.) were heated on a steam bath for 5 minutes. Excess acetic anhydride was removed by evaporation and the residue dissolved in ethyl acetate. 40—60°C petrol was added, followed by crystallisation under cool conditions to give a yield of 0.5 g., m.p. 125°C.

The melting point remained constant on recrystallisation (ethyl acetate/petrol 40—60°C).

b) *Tetraacetyl derivative*

The triazine (1.0 g.), triethylamine (5 ml.) and redistilled acetic anhydride (10 ml.) were stirred at room temperature for 70 hours. The reaction mixture was poured onto ice and stirred for 1 hour followed by extraction with ethyl acetate. Extracts were washed with water, dried over $MgSO_4$, decolourised with charcoal and solvent removed by evaporation. The residue was recrystallised from ethyl acetate/petrol 40—60°C.

Yield=0.4 g., m.p. 84°C.

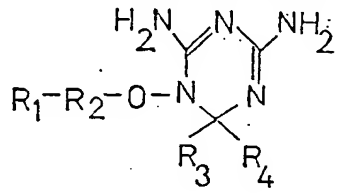
On recrystallisation (ethyl acetate/petrol 40—60°C) m.p. = 85°C.

c) *Di-benzamide*

The triazine (2.0 g.) and benzoic anhydride (10 g.) were heated in a steam bath for 30 minutes. The reaction mixture was cooled and triturated with ether to give a white solid, m.p. 128—130°C.

WHAT WE CLAIM IS:—

1. N-substituted symmetrical dihydro triazine derivatives of general formula



where R_1 is an aromatic ring system, a heterocyclic group or a non aryl carbocyclic ring system of 3—8 carbon atoms, all of which rings may be substituted or unsubstituted;

R_2 is a substituted or unsubstituted divalent aliphatic group of 2—16 carbon atoms;

R_3 is hydrogen or lower alkyl of 1—4 carbon atoms and

R_4 is lower alkyl of 1—4 carbon atoms, where R_3 and R_4 may be the same or different or may be linked to form a spirocycloalkane or lower-alkylspirocycloalkane group including the 2-carbon of the triazine ring

and salts and acyl derivatives thereof, except that R_1 is not an unsubstituted phenyl group when R_2 is unsubstituted and that R_1 is not 1 - methyl - 2 - naphthyl when R_2 is ethylene.

2. A compound as claimed in claim 1 in which R_1 is phenyl or naphthyl both of which may be substituted or unsubstituted.

3. A compound as claimed in claim 2 in which R_1 is substituted by one or more halogen atoms.

4. A compound as claimed in claim 3 in which the halogen is chlorine.

5. A compound as claimed in any one of the preceding claims in which R_2 is saturated aliphatic.

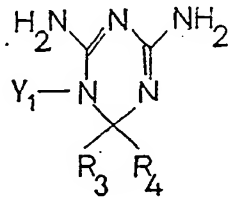
6. A compound as claimed in claim 5 in which R_2 is straight chain alkylene of 2—8 carbon atoms.

7. A compound as claimed in any one of the preceding claims in which R_3 and R_4 are both methyl.

8. 4,6 - diamino - 1,2 - dihydro - 2,2 - dimethyl - 1 - [3 - (3,4 - dichlorophenyl)propyloxy] - 1,3,5 - triazine hydrobromide.

9. A compound as claimed in claim 1 in which R_1 is a substituted aryl ring system (except when R_2 is substituted in which case R_1 may be substituted or unsubstituted) or a substituted or unsubstituted heterocyclic group or a substituted or unsubstituted cycloalkyl group of 3—8 carbon atoms and R_2 is a divalent aliphatic hydrocarbon radical containing 2—16 carbon atoms which may be straight chain or branched and mono or poly substituted by hydroxyl, methoxy or halogen which may be the same or different.

10. A process for the preparation of a compound as claimed in any one of the preceding claims which comprises reacting a triazine



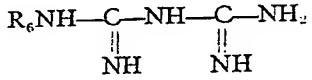
where Y_1 is a reactive group with a compound R_5Y_2 which is capable of reacting with Y_1 so as to form the group $R_1—R_2—O—$ or an intermediate group capable of conversion thereto and where necessary converting the intermediate group to $R_1—R_2—O—$ and optionally where necessary forming a salt.

11. A process as claimed in claim 10 in which Y_1 and Y_2 are OH or reactive derivatives thereof at least one of which contains an oxygen atom.

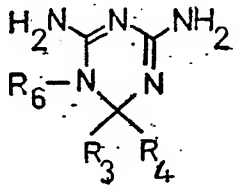
12. A process as claimed in claim 11 in which Y_1 is OH and Y_2 is chlorine, bromine or iodine.

13. A process as claimed in any one of claims 10—12 in which R_5 is $R_1—R_2—$.

14. A process for the preparation of a compound as claimed in any one of claims 1—9 which comprises reacting a substituted diguanide of formula



where R_6 is $R_1—R_2—O—$ or a group capable of conversion thereto, with a carbonyl compound R_3R_4CO in the presence of an acid catalyst to form a compound

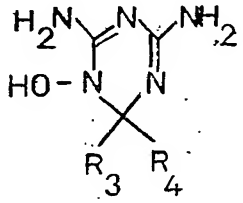


and where necessary converting R_6 into $R_1—R_2—O$ and optionally where necessary forming a salt.

15. A process as claimed in claim 14 in which R_6 is $R_1—R_2—O—$.

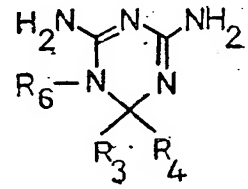
16. A process as claimed in claim 14 or claim 15 in which the acid catalyst is a strong acid and in which the reaction is performed in the presence of an inert solvent or diluent.

17. A process as claimed in claim 14 in which R_6 is capable of hydrogenolysis to OH which comprises forming a compound



and subjecting this to hydrogenolysis to convert R_6 to OH.

18. A process as claimed in claim 17 in which R_6 is a group capable of conversion to OH and which comprises converting R_6 to OH to form a compound of formula



and then reacting this with a compound $R_1R_2Y_3$ where Y_3 is a reactive group displacable by a nucleophilic group to form the compound in which $R_1—R_2—O$ replaces R_6.

19. A process as claimed in claim 17 in which R_6 is substituted or unsubstituted benzyloxy or naphthylmethyloxy.

20. A process as claimed in claim 18 or claim 19 in which the hydrogenolysis is performed by treatment with hydrogen in the presence of a palladium catalyst.

21. A process as claimed in any one of claims 10—20 which comprises the additional step of reacting the product with an acylating reagent to form an acyl derivative.

22. A process as claimed in claim 21 in which an acetylating reagent is used.

23. A substituted triazine when made by a process as claimed in any one of claims 10—20, 21 or 22.

24. A pharmaceutical composition for use in the treatment or prevention of malaria which comprises a compound as claimed in any one of claims 1—9 or 23 in combination with a pharmaceutically acceptable carrier.

25. A composition as claimed in claim 24 which also contains another anti-malarial.

26. A composition as claimed in claim 25 in which the other anti-malarial is a sulphonamide.

27. A compound as claimed in claim 1 and as described in any one of examples 1—43.

28. A process for the preparation of a compound as claimed in claim 1 and as described in any one of examples 1—43.

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